pharmaceutically acceptable buffer, said suspension being suitable for parenteral administration.

73. The pharmaceutical composition of claim 72 wherein said zinc salt is zinc chloride.

74. The pharmaceutical composition of any of claims 66, 67 or 72 wherein said peptide is amylin.

75. The pharmaceutical composition of any of claims 66, 67 or 72 wherein said peptide is selected from the group consisting of deamidated amylin and reduced amylin, alone or in conjunction with amylin.

CHANGES TO THE SPECIFICATION

The specification has been amended as indicated for ease of reference to amylin and amylin which has no carboxy-terminal amide, or "deamidated amylin." No new matter has been added.

Claims 1, 5, 19, 22, 24-28, 32, 33, 41 and 42 have been cancelled and corresponding claims 46-75 have been added in accordance with the Examiner's suggestion that the claims more clearly reflect that they are directed to pharmaceutical compositions and methods of their preparation.

Newly added claims 46-75 find support throughout the specification and in original claims 1-45. For example, claims 46-55 find support in original claim 1, claims 56-65 find support in original claim 5, claim 66 finds support in original claim 19, claim 67 finds support in original claim 22, claims 69-71 find support in original claims 24-28, claims 72 and 73 find support in original claims 32 and 33, and claims 74 and 75 find support in original claims 1, 5, 41 and 42.

RESPONSE TO REJECTIONS

1. Section 101 - Nonstatutory Subject Matter Rejection

Claims 1, 5, 19, 22, 24-28, 32, 33, 41 and 42 stand rejected under § 101 on the ground that they are directed toward nonstatutory subject matter. Applicant agrees with the Examiner's statement that a product of nature is unpatentable without some alteration such as increased purity or increased biological activity. In this instance, however, the claimed compounds have been so altered as reflected in newly rewritten claims 46-55 and 67-75.

Amylin has been isolated from the naturally occurring amyloid masses found in pancreases of type 2 diabetic humans (specification p. 2, lines 16-19), thus, it has increased purity over the naturally occurring amylin and the amyloid masses. See, for example, specification p. 11, lines 12-22: "To purify amylin from various different sources to a level useful in human therapeutics, various methods have been used. It has been demonstrated that amylin can be isolated from the human pancreas in a highly pure state by a combination of concentration using a centrifuge, gel filtration chromatography, and reverse phase chromatography, specifically HPLC." Applicant has noted that the efficacy of an amylin preparation in the treatment of diabetes mellitus is reflected in the solubility of amylin (specification, p. 8, lines 6-9). Thus, the present invention relates to an altered product having increased biological activity, as well as increased purity.

2. Section 101 - Lack of Utility Rejection

The Examiner has rejected claims 1, 5, 19, 22, 24-28, 32-33 and 41-42 "because the invention as disclosed is inoperative and therefore lacks utility" on the grounds that the "disclosure contains no factual data (experimental or clinical or effective dosage) that supports the alleged utility." (March 15, 1990 Office Action, p. 4).

We respectfully disagree and direct the Examiner's attention to applicant's specification (at pp. 12-13) and the experiments described which show that amylin reduces the rate of glycogen synthesis in rat soleus muscle strips. The results of these experiments demonstrate that amylin prevents the processing of glucose into glycogen at both basal and stimulatory levels of insulin (specification p.12, lines 6-8). Thus, amylin appears to modulate and reduce the hypoglycemic effects of insulin, both by reducing the amount of insulin released in response to a given glucose stimulus and by reducing the rate of conversion of glucose into glycogen (specification p.7, lines 27-28; p.8, lines 1-3).

Type 1 diabetes results from destruction of islet B cells. Because amylin modulates and reduces the hypoglycemic effects of insulin, and amylin (like insulin) is produced in islet B cells, it appears that type 1 diabetes is associated with a deficiency in amylin as well as a deficiency in insulin (specification p.6, lines 5-14). Thus, the results of the experiments described in applicants' specification demonstrate that co-administration of amylin with insulin may avoid the serious side effect of hypoglycemia associated with treatment with insulin alone (specification p.1, lines 8-14; p.6, lines 11-27).

Thus, the specification adequately supports applicant's claims for treatment of diabetes and hypoglycemia. Since this application was filed, furthermore, additional published studies have confirmed that amylin exerts potent effects to modulate insulin's actions on the key target tissues of liver and skeletal muscle. Excessive sensitivity to insulin action, resulting in excessive post-insulin uptake into skeletal muscle and also excessive reduction in hepatic glucose output, are the mechanisms whereby hypoglycemia occurs following therapeutic administration of insulin. A lack of amylin will exacerbate this tendency, and expose the amylin-deficient patient with type 1 diabetes mellitus, for example, to excessive risk of insulin-induced hypoglycemia. Applicant Cooper discovered that the replacement of amylin along with insulin will alleviate the tendency of amylin-deficient individuals to hypoglycemia, as described and claimed herein.

As noted in the preface to "Joslin's Diabetes Mellitus" one of the most authoritative texts on diabetes mellitus, there is now a widely recognized need for maintenance of normal blood glucose levels (euglycemic control) in the insulin-treatment of diabetes mellitus:

> The most important of these [recent developments in the therapy of diabetes mellitus] is the wider acceptance by those interested in diabetes of the concept that careful control of the blood glucose provides the best insurance currently available for the prevention, amelioration, or postponement of the dread complications of angiopathy and neuropathy in their varied manifestations. This concept is eminently logical and is used in the treatment of other diseases with the aim of restoring bodily structure and function or toward normal insofar as possible. A deterrent to greater acceptance of this principle in diabetes has been the lack of controlled, prospective, clinical studies indicating a positive relationship between the degree of metabolic control and

> extent of late complications. Fortunately, enough information has become available during the past several years to convince most clinicians and investigators as to the benefits of control.

Marble, A., et al. eds. Joslin's Diabetes Mellitus, pp. vii (Lea & Febiger, Philadelphia, PA, 1985).

Hypoglycemia is the major adverse effect of insulin therapy and a primary factor preventing the attainment of euglycemic control in the insulin therapy of type 1 diabetes. In 1989, Zinman wrote that "Hypoglycemia is by far the most serious and common adverse reaction to the administration of insulin, and it can result in substantial morbidity and death." According to Zinman, "These observations underscore the fact that the major barrier in striving for normoglycemia with intensified regimens of insulin treatment is the increased risk of severe hypoglycemia. This was well demonstrated in the feasibility report of the Diabetes Control and Complications Trial, in which patients who were intensively treated had a twofold to threefold increase in the occurrence of severe hypoglycemia." Zinman, B., "The physiologic replacement of insulin. An elusive goal," N. Engl. N. Med., 321:363-370 (1989).

Another group confirmed still earlier that "The most common and potentially most serious complication of insulin treatment is hypoglycemia. Hypoglycemia may be produced with any dose or preparation of insulin if the amount of insulin administered is excessive relative to the availability of glucose from endogenous and exogenous (e.g. dietary) sources. ... Insulin-induced hypoglycemia is experienced at some time by virtually all type 1 diabetics. In some series, severe hypoglycemia (necessitating hospitalization or assistance from

another person) has been observed in 25% of all patients over a 1-year period. In addition, hypoglycemia accounts for 3 to 7 percent of deaths in patients with type 1 diabetes." Shafrir, E., et al. in Felig, P., Baxter, J.D., Broadus, A.E. & Frohman, L.A. "Endocrinology and Metabolism." pp. 1043-1178 (1987). (2nd ed. McGraw-Hill, New York, NY) (emphasis by applicants).

A combined statement of the leading experts in the field of hypoglycemia from the International Diabetes Federation World Congress (1988) expresses this same concern: "Hypoglycemia causes substantial morbidity and some mortality in insulin-dependent diabetes mellitus (IDDM). It is often the limiting factor in attempts to achieve euglycemia. . . Fundamentally, pending the prevention or cure of IDDM, we must learn to deliver insulin in a much more physiological fashion, or to prevent, correct, or compensate for compromised glucose counterregulation if we are to achieve euglycemia safely in most patients with IDDM." Cryer, P.E., et al. "Hypoglycemia in IDDM," Diabetes 38:1193 (1989). This understanding was summarized in another report as follows:

> "Hypoglycemia is a frequent complication of the treatment of IDDM. It is the most frequent morbid event in IDDM. Its incidence is increased two- to threefold during intensive therapy that effectively lowers plasma glucose concentrations to near-normal levels. Indeed, it is often the limiting factor in attempts to achieve euglycemia.
>
> Although rates vary among individuals, patients practicing conventional therapy suffer an average of about 1 episode of symptomatic hypoglycemia per week, whereas those practicing intensive therapy suffer about 2 such episodes per week. Thus, over 40 yr of IDDM, the average patient can be projected to experience 2000-4000 episodes of symptomatic hypoglycemia. Approximately 10% of patients practicing conventional therapy suffer at least 1 episode of severe hypoglycemia, i.e. requiring assistance from others, including glucose or glucagon

> administration and episodes with seizure or loss of consciousness, in a given year. This figure is about 25% among patients practicing intensive therapy. In one large, prospective randomized study, the corresponding event rates were 0.17 and 0.54 episodes of severe hypoglycemia per patient per year during conventional and intensive therapy respectively."

Cryer, P.E., et al. "Hypoglycemia in IDDM," Diabetes 38: 1193-1198 (1989). In another study, "Overnight metabolic studies in 39 poorly controlled (high blood glucose levels) insulin-treated diabetic patients aged 9 to 66 years showed hypoglycemia (blood glucose <2 mmol/l) in 22 patients; it lasted 3 h or more in 17." Gale, E.A.M. & Tattersall, R.B. "Unrecognized hypoglycemia in insulin-treated diabetics," Lancet i, 1049-1052 (1979).

The two major forms of diabetes mellitus in humans are insulin-dependent (type 1) diabetes mellitus (IDDM), and non-insulin-dependent (type 2) diabetes mellitus (NIDDM). Although both may be treated with insulin, the former is distinguished by an absolute requirement for insulin therapy to prevent early death produced by absolute insulin-lack.

With regard to current research into type 1 diabetes, there are numerous well-characterized and well-accepted animal models for the disease, which fall into two general classes. The first are animals which suffer spontaneous onset of insulitis leading to destruction of their pancreatic islet ß-cells, and consequent IDDM-like disease. Main examples include the BB/Wor rat (Mordes, J.P., et al., "The BB rat," Diabetes/Metabolism Rev. 3, 725-750 (1987)) and the NOD (non-obese diabetic) mouse (Kolb, H.) "Mouse models of insulin dependent diabetes: low-dose streptozotocin-induced diabetes and non-obese diabetic (NOD) mouse," Diabetes/Metabolism Rev. 3, 751-778 (1987)).

The second established model includes animals in which an IDDM-like disease is induced by chemical ß-cell toxins. Examples of the latter type include mammals treated with low-dose streptozotocin (STZ) (ibid) or alloxan. Both models are very close in most respects to human disease of type 1.

It has now been demonstrated that amylin and insulin are co-expressed and co-secreted from islet ß-cells. Leffert, J.D., et al., "Rat amylin: cloning and tissue-specific expression in pancreatic islets." Proc. Natl. Acad. Sci. USA 84, 3127-3130 (1989); Ogawa, A. et al., supra; Roberts, A.N. et al., "Molecular and functional characterization of amylin, a peptide associated with type 2 diabetes mellitus," Proc. Natl. Acad. Sci. USA 86, 9662-9666; Cooper, G.J.S. et al., "Amylin and the amylin gene: structure, function and relationship to islet amyloid and to diabetes mellitus," Biochim. Biophys. Acta 1014, 247-258 (1989); Fehman, H.C., et al. "Cosecretion of amylin and insulin from isolated rat pancreas," FEBS Lett. 262, 279-281 (1989).

Recent publications have also confirmed that amylin expression and secretion are destroyed in a widely accepted animal model of IDDM, and that circulating levels of amylin are deficient in the blood of human patients with IDDM. Amylin expression is destroyed in rats injected with low-dose Streptozotocin, at both the level of transcription of the amylin gene and expression of the protein in the pancreas, and also at the level of amylin secretion from the pancreas. Ogawa, A., et al., "Amylin secretion from the rat pancreas and its selective loss after streptozotocin treatment," J. Clin. Invest. 85, 973-976; Inman, L., et al., "Pancreatic beta cell expression of amylin in streptozotocin-induced diabetes in mice," Diabetes 39 (Suppl. 1) 143A (1990). Thus, production and secretion of amylin

in the pancreas of rats which have IDDM-like disease is destroyed in two separate animal models.

In aother published report, human patients with IDDM had reduced or absent levels of amylin circulating in the blood. In one study, amylin-immunoreactivity was undetectable in 6 patients with IDDM, compared with 13 non-diabetic controls Ludvik, B., et al., "Basal and stimulated plasma amylin levels in diabetes mellitus," Diabetes 39 (Suppl. 1) 116A (1990).

The material reviewed above shows that the destruction of amylin production and secretion occurs in relevant animal models of IDDM. It also provides evidence for the frequent occurrence of amylin-deficiency in human patients with IDDM. Therefore, IDDM, i.e., that is an amylin-deficient state.

Amylin has been shown to exert potent effects on muscle glucose metabolism in vitro and in vivo, and has been shown to exert biological effects in liver and skeletal muscle consistent with those observed in the insulin resistance of Type 2 diabetes mellitus. As noted, reduced amylin levels in IDDM will make the body excessively sensitive to insulin action, thereby promoting insulin-induced hypoglycemia, as observed in the insulin therapy of IDDM. Co-administration of amylin with insulin will protect against excessive insulin action and insulin-induced hypoglycemia.

Amylin effects in skeletal muscle and liver in vitro are briefly summarized. In vitro, amylin acts on skeletal muscle to produce reduced glucose uptake, and reduced incorporation of glucose into glycogen. In white skeletal muscle, amylin selectively increases rates of glycogenolysis, which leads to increased release of lactate. Cooper, G.J.S et al., "Purification and characterization of a peptide from amyloid-rich

pancreases of type 2 diabetic patients," Proc. Natl. Acad. Sci. USA 84, 8628-8632 (1987). Amylin acts to potently stimulate rates of gluconeogenesis and glycogenolysis in the liver in vitro. This leads to increased mobilisation of cellular glycogen stores and to increased rates of hepatic glucose output. Cooper, G.J.S et al., "Amylin found in amyloid deposits in human type 2 diabetes mellitus may be a hormone that regulates glycogen metabolism in skeletal muscle,"Proc. Natl. Acad. Sci. USA. 85, 7763-7766 (1988); Leighton, B. & Cooper, G.J.S., "Pancreatic amylin and calcitonin gene-related peptide cause resistance to insulin in skeletal muscle in vitro," Nature 335, 632-635 (1988); Cooper, G.J.S., Willis, A.C. & Leighton, B., "Amylin hormone," Nature 340, 272 (1989); Cooper, G.J.S. et al., "Amylin and non-insulin-dependent (type 2) diabetes mellitus," in Larkins, R., Zimmett, P. & Chisholm, D., eds. Diabetes (Elsevier, Amsterdam, Netherlands), pp. 493-496; Cooper, G.J.S. et al. Biochem. Biophys. Acta, supra (1988); Leighton, B., Foot, E.A. & Cooper, G.J.S., "The effects of calcitonin gene-related peptide and amylin on glycogen metabolism in muscle are dependent on muscle fibre type," Diabetic Med. 6, Suppl. 2, A4 (1989); Kreutter, D., Orena, S.J. & Andrews, G.C., "Induction of insulin resistance by amylin in isolated soleus muscle and cultured myocytes," Diabetes 39 (Suppl. 1) 121A (1990); Ciaraldi, T.P., Cooper, G.J.S. & Stolpe, M., "In vitro effects of amylin on carbohydrate metabolism," Diabetes 39 (Suppl. 1) 149A; Leighton, B. & Cooper, G.J.S., "The role of amylin in the insulin resistance of non-insulin-dependent diabetes mellitus," Trends Biochem. Sci. 15, 295-299 (1990).

Amylin has been shown to produce increased rates of hepatic glucose output from the liver in vivo, even in the

presence of maximally stimulating levels of insulin. Amylin also to decreases rates of glucose uptake into the periphery (skeletal muscle) and thereby promotes a buffering of insulin action. The hormone also produces a stimulation of lactate output from peripheral tissues, and, when injected into rats, is capable of counteracting insulin action. Molina, J.M. et al. Induction of insulin resistance in vivo by amylin and calcitonin gene-related peptide," Diabetes 39, 260-265 (1990); Koopmans, S.J. et al., "Pancreatic amylinamide induces in vivo hepatic and peripheral insulin resistance in the rat," Diabetes 39 (Suppl. 1) 101A (1990); Young, D.A. et al., "Effect of amylin on glucose utilization during euglycemic-hyperinsulinemic clamps," Diabetes 39 (Suppl. 1) 116A (1990).

The Examiner not provided support for his statement that "[s]ince the products are intended for in vivo treatment, applicants must have data showing operability in vivo." Under the test set forth in a number of cases, e.g., In re Langer, 501 F.2d 1380, 183 U.S.P.Q. 288, 297 (C.C.P.A. 1974), the Examiner must take the disclosed utility as sufficient unless those skilled in the art would doubt the truth or scope of the utility. As shown by the foregoing, it is submitted that the utility of amylin or amylin agonist therapy in diabetes and hypoglycemia is adequately established, both conceptually and scientifically, and we request tht this rejection be withdrawn.

3. Section 112, First Paragraph

a. How-to-use (effectiveness/utility)

The Examiner's first objection under section 112, i.e., that the disclosure does not enable one skilled in the art to use the claimed invention effectively for treating diabetes, relates

to effectiveness and therefore is an issue with respect to utility, which is discussed in Section 2 above. For reason there set forth, this objection should be withdrawn.

b. How-to-make

The Examiner contends that the specification "is not enabling as to the preparation and identification of the active subfragment(s), conservative variants or function[al] peptides o[f] amylin."

It is well established that enablement under § 112 requires that the specification teach those skilled in the art to make and use the invention without undue experimentation. E.g., Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1384, 231 U.S.P.Q. 81, 94 (Fed. Cir. 1986), cert. denied, 107 S. Ct. 1606 (1987). However, "[e]nablement is not precluded by the necessity for some experimentation, such as routine screening." In re Wands, 858 F.2d 731, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988). Although the practice of the claimed invention must not require undue experimentation, "the key word is 'undue,' not 'experimentation.'" 8 U.S.P.Q. 2d at 1404.

The standard for determining what constitutes undue experimentation is reasonableness, considering among other things the nature of the invention and the state of the art. "The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." Id. (quoting In re Jackson, 217 U.S.P.Q. 804, 807 (Bd. App. 1982)).

Applicant's specification clearly defines the terms "functional peptide fragment" and "conservative fragment." "A functional peptide fragment of amylin or amylin-NH_2 or CGRP is meant to include a peptide fragment of at least 5 amino acid residues in length, which performs in vivo a therapeutic function of the complete amylin or amylin-NH_2 or CGRP peptide" (specification p.5, lines 2-5). "A conservative variant is meant to include [a] peptide which is substantially, though not completely, homologous with amylin or amylin-NH_2 or CGRP or fragments thereof, but which is functionally equivalent thereto" (specification p.5, lines 5-9). The state of the art of peptide chemistry has advanced to the point that the experimental procedures for altering and synthesizing peptides are routine. Thus, given the disclosure in the specification concerning the functions of amylin and the experiments described in the Example for testing for amylin's activity, it is apparent that one skilled in the art could easily synthesize functional peptide fragments and conservative variants.

c. How-to-use

The Examiner states that applicant's disclosure is not enabling with respect to the use of amylin and CGRP peptides. The issue is whether applicant's disclosure is sufficient, coupled with information known in the relevant art, to enable one skilled in the appropriate art to use the claimed inventions. Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1384, 231 U.S.P.Q. 81, 94 (Fed. Cir. 1986), cert. denied, U.S. S. Ct. (1987). As previously noted, a specification may be enabling even though experimentation is required, provided that the experimentation is not undue.

Applicant has provided extensive information in the specification concerning the use of the claimed compounds to treat diabetes mellitus and/or hypoglycemia. The specification describes treatment methods involving in a preferred aspect, co-administration of insulin and either amylin, amylin-NH_2, CGRP or subpeptides thereof, including general formulations as to ratio of insulin to amylin, amylin-NH_2 or CGRP (specification p.5, lines 13-28; p.6, lines 1-5).

In addition, applicant has supplied information regarding techniques for preparing soluble preparations of amylin, amylin-NH_2, CGRP and subpeptides thereof (specification p.8, lines 9-23). The specification also describes methods of increasing biological activity of synthetic amylin (specification p.8, lines 24-28; p.9, lines 1-26).

The subject of methods of preparing amylin compounds to provide varying durations of action (specification, p.9, lines 29-30; p.10, lines 1-28; p.11, lines 1-6), as well as methods of stabilizing amylin preparations (specification, p.11, lines 7-11), are also discussed.

Thus, although some experimentation will be required to determine exact method of treatment of diabetes mellitus and/or hypoglycemia by using applicant's claimed inventions, this is understood to be the case for any therapeutic which will enter clinical trials. The extensive disclosure in the specification, however, combined with the level of skill in the art, indicate that such experimentation will be routine.

4. <u>§ 102/§ 103</u>

Claims 1, 22, 41 and 42 stand rejected as either anticipated by or, in the alternative, obvious over any of these

publications: (1) Cooper et al., "Purification and Characterization of Peptide from Amyloid-Rich Pancreases of Type 2 Diabetes Patients," PNAS 84:8628 (December 1987); (2) Clark et al., "Islet Amyloid Formed From Diabetes-Associated Peptide May Be Pathenogenic in Type-2 Diabetes," Lancet 8554:231 (August 1987); or (3) Westermark et al., "Amyloid Fibrils in Human Insulinoma and Islets of Langerhans of the Diabetic Cat are Derived From a Neuropeptide-like Protein Also Present in Normal Islet Cells," PNAS 84:3881 (June 1987). We respectfully traverse the Examiner's anticipation/obviousness rejection and request reconsideration, based on the following:

a. Cooper

The Cooper et al. article referred to by the Examiner was published in December of 1987, well after the U.K. priority date of August 26, 1987, and therefore, as a matter of laws neither anticipates applicant's inventions nor renders them obvious. Applicant has ordered and will submit a certified copy of the U.K. specification and requests that this rejection be withdrawn.

b. Clark

The Clark et al. publication, on which applicant is a co-author, states that DAP "may be a factor leading to the abnormal insulin secretion of type-2 diabetes," and suggests that "[p]ancreatic amyloid may result from excess secretion of DAP associated with abnormal B-cell function in type-2 diabetes" (p.233). However, the article makes no suggestion that amylin, or a combination of insulin and amylin, may be used to treat diabetes mellitus and/or hypoglycemia, as described and claimed

in the instant application. The Clark et al. article also lacks any suggestion that amylin functions to modulate the rate of glucose-induced insulin secretion from B-cells and to reduce the rate of glycogen synthesis in rat skeletal muscles, as shown by applicant herein (specification p.7, lines 12-19).

The only mechanism of action postulated by the Clark article is that, "[a]myloid, deposited between the endocrine cells and the islet capillaries could disrupt the passage of glucose and hormones to and from the islet cells, leading to the abnormalities in control of hormone secretion that are characteristic of type 2 diabetes." No mention of Type 1 diabetes or hypoglycemia is made. Accordingly, applicant requests that this rejection also be withdrawn as neither the methods of treatment nor the pharmaceutical compositions described and claimed herein are set forth or suggested.

c. Westermark

The Westermark et al. publication is even less pertinent than the Clark et al. reference as Westermark et al. do not set forth the correct or complete sequence of amylin. They set forth only a partial sequence of an apparently similar peptide, and one that was incompletely isolated from an insulimoma (an insulin-producing tumor), not from the pancreas. Further, Westermark et al. at several places in the article declare themselves to be completely ignorant of the function the molecule (see, for example, the Abstract and page 3884), whatever it was.

For these reasons the rejection of claims under §§ 102 and 103 should be withdrawn.

5. § 112, Second Paragraph

Claims 1, 5, 19, 22, 24-28, 32, 33, 41 and 42 stand rejected under 35 U.S.C. § 112, second paragraph. We respectfully request that this rejection be withdrawn upon reconsideration by the Examiner.

The terms "functional peptide fragment" and "conservative variant" are clearly defined in the specification at page 5. "A functional peptide fragment of amylin or amylin-NH_2 or CGRP is meant to include a peptide fragment of at least 5 amino acid residues in length, which performs in vivo a therapeutic function of the complete amylin or amylin-NH_2 or CGRP peptide. A conservative variant is meant to include [a] peptide which is substantially, though not completely, homologous with amylin or amylin-NH_2 or CGRP or the fragments thereof, but which is functionally equivalent thereto (specification p. 5, lines 2-9). Furthermore, the pending claims specify only those peptide fragments and conservative variants that have amylin-like activity.

Respectfully submitted,

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